UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	9

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/203,676	Zalutsky
Examiner	**Group Art Unit**
Karen Canella	1642

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3 months* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-43* is/are pending in the application.

Of the above, claim(s) *22-43* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election of group I in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-43 are pending.

Claims 22-43 drawn to non-elected Inventions are withdrawn from consideration.

Claims 1-21 are examined on the merits.

Drawings

3. The drawings are objected to because of the reasons set forth on the enclosed PTO-948 form. Correction is required.

Claim Objections

4. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of claim 1. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 2 recites the limitation "...wherein the oligopeptide comprises two or more L-amino acids, the L-amino acids are separated from one another by one or more positively charged amino acids". Independent claim 1 recites the condition "...wherein the oligopeptide does not comprise two or more contiguous L-amino acids." There is insufficient antecedent basis for the limitation of having two or more L-amino acids separated from each other by a positively charged amino acid(s) in the claim since the parent claim precludes this situation.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 2, 3, 4 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 2 recites "...wherein the oligopeptide comprises two or more L-amino acids, the L-amino acids are separated from one another by one or more positively charged amino acids". The stereochemistry of the positively charged amino acid is not defined. For purposes of examination, it will be assumed that either a positively charged D-amino acid or a positively charged L-amino acid will suffice as a spacer between L-amino acids not carrying a positive charge.

-Claim 3 is unclearin depicting how the moiety of formula (II) is bound to the oligopeptide.

-Claim 6 is unclear in reciting "chimeric" as the exact meaning of the word is not known. The term chimeric is generic to a class of antibodies which are products of genetic shuffling of anibody domains and other active proteins. The term encompasses antibodies fused to non-immunoglobin proteins as well as antibodies wherein any domain of the antibody is substituted by corresponding regions or residues of human antibodies included but not limited to CDR grafted antibodies. In the absence of a single defined art recognized meaning for the phrase, and lacking definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 1, 5, 8, 14, and 17-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Govindan (Journal of Nuclear Medicine, abstract, May 1998). Claims 1, 5, 8, 14, and 17-20 are drawn to a composition for internally labeling a cell comprising a ligand which specifically binds to an internalizing cell surface tumor receptor, said ligand being covalently bound to I-131 labeled oligopeptide comprising at least one D-Lys, and one positively charged amino acid. Govindan discloses compositions for radioimmunotherapy comprising internalizing lymphoma and internalizing lung adenocarcinoma monoclonal antibodies covalently linked to a radio-iodinated oligopeptide consisting of three to four D-amino acids, with a D-lysine amino acid at the terminus. Thus Govindan discloses different internalizable monoclonal antibodies covalently linked with a radionuclide via an oligopeptide linkage containing at least on D-amino acid, one positively charged amino acid, without contiguous L-amino acids, which is exactly the same as claimed.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawai (WO 90/09162) in view of Kindzelskii (J of Structural Biology, 1994). Claims 1 and 21 are drawn to a ligand covalently attached to a oligopeptide containing a D-amino acid and a positively charged amino acid, carrying a fluorescent label. Kawai teaches oligopeptides which are ligands for the anaphylatoxin receptor (C3a, C4a and C5a) which are internalized by the receptor and contain up to three D-amino acids (pg 24, lin 32 to pg 25, line 5). Example 87 of Kawai (pg 62) recites the oligopeptide (D-Alanyl)-Leucyl-(D-Alanyl)-Arginyl-OH, which has one positively charged amino acid, two D-amino acids and no contiguous L-amino acids. Kawai does not teach the fluorecent labeled oligopeptide. Kindzelskii teaches the fluorescent label on oligopeptides which contain D-amino acids and bind to internalizing membrane receptors on neutrophiles (pg. 191, column , line 9). It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to label the oligopeptide ligand for the anaphylatoxin receptor as taught by Kawai with a fluorescent label as taught by Kindzelski. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Kindzelskii on the effectiveness of the fluorescent label for visualizing the spatial distribution of membrane receptors.

11. Claims 1-5, 8, 14 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Govindan (Journal of Nuclear Medicine, abstract, May 1998) in view of any of Zalutsky (USPN 5,302,700) or Zalutsky (CRISP Abstract, 1994). Claims 1-5, 8 and 17-20 are drawn to a composition for internally labeling a cell comprising a ligand which specifically binds to an internalizing cell surface tumor receptor, said ligand being covalently bound to I-131 labeled oligopeptide via a labeling moiety of 3-iodobenzoate or 3-(tri-n-butylstannyl)benzoate), comprising at least one D-Lys, and one positively charged amino acid. Govindan teaches compositions for radioimmunotherapy comprising internalizing lymphoma and internalizing lung adenocarcinoma monoclonal antibodies covalently linked to a radio-iodinated oligopeptide

consisting of three to four D-amino acids, with a D-lysine amino acid at the terminus. Govidan does not teach the specific labeling moieties of 3-iodobenzoate or 3-(tri-n-butylstannyl)benzoate). Zalutsky or Zalutsky teach the radioiodination of peptides via the specific labeling moieties of 3-iodobenzoate(CRISP Abstract, 1994) or 3-(tri-n-butylstannyl)benzoate) (USPN 5,302,700, column 3, line 13-15). It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize the labeling moieties of 3-iodobenzoate or 3-(tri-n-butylstannyl)benzoate) as taught by Zalutsky or Zalutsky. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Zalutsky or Zalutsky on the preservation of biological activity of the protein or antibody accepting the label in cases where 3-iodobenzoate or 3-(tri-n-butylstannyl)benzoate) is used in place of direct iodination methods (USPN 5,302,700, column 1, lines 33-65).

12. Claims 1, 3-5, 8-10, 14 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reist (Cancer Research, 1996) in view of Govindan (Journal of Nuclear Medicine, May 1998). Claims 1, 5, 8-10 and 17-20 are drawn to a composition comprising a monoclonal antibody that specifically binds EGRFvIII which is covalently attached to a oligopeptide containing a D-amino acid and a positively charged amino acid, carrying an I-125 or I-131 via a 5-iodo-3-pyridinecarboxylate. Reist teaches a composition comprising iodine 131 or iodine 125 in a 5-iodo-3-pyridine carboxylate labeled (pg 4970, column 2, 4th lines from bottom) monoclonal antibody against the EGFRvIII (pg 4970, column 2, lines 7-8 from bottom). Reist also teaches the benefits of carrying a positively charged moiety for resisting lysosomal degradation and enhancing cellular retention of the radiolabel (pg 4970, column 1, lines 7-15). Reist does not specifically teach D-amino acids and positively charged amino acids for resisting lysosomal degradation. Govindan teaches compositions for radioimmunotherapy comprising an internalizing antibodies covalently linked to a radioiodinated oligopeptide consisting of three to four D-amino acids, with a D-lysine amino acid at the terminus. It would have been *prima facia*

obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Reist and Govindan in a composition comprising a monoclonal antibody that specifically binds EGRFvIII which is covalently attached to a oligopeptide containing a D-amino acid and a positively charged amino acid, carrying an I-125 or I-131 via a 5-iodo-3-pyridinecarboxylate moiety covalently linked to the oligopeptide. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the general teachings of Reist on the desirability of attaining resistance to lysosomal degradation by means of a positively charged moiety and the specific teachings of Govindan on the success of compositions for radioimmunotherapy comprising an internalizing antibodies covalently linked to a radioiodinated oligopeptide consisting of three to four D-amino acids, with a D-lysine amino acid at the terminus, in delivering a greater dose of radioiodine to tumors targeted by the monoclonal antibodies.

13. Claims 1, 3-5, 8-10, 14 and 17-20 rejected under 35 U.S.C. 103(a) as being unpatentable over Reist (Cancer Research, 1996) and Govindan (Journal of Nuclear Medicine, May 1998) as applied to claims 1, 3-5, 8-10, 14 and 17-20 above, and further in view of Emery (Antibody Engineering, 1995). Claims 1, 5, 7-10 and 17-20 are drawn to a composition comprising a humanized antibody that specifically binds EGRFvIII which is covalently attached to a oligopeptide containing a D-amino acid and a positively charged amino acid, carrying an I-125 or I-131 via a 5-iodo-3-pyridinecarboxylate. Reist and Govidan do not teach the use of the humanized antibody that specifically binds EGFRvIII. Emery teaches that the use of humanized vs. mouse antibodies in human clinical studies increases the half-life of the antibodies, imparts greater effector functions by means of the human framework constant regions and avoids human anti-mouse hypersensitivity reactions. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to humanize the monoclonal antibody that specifically binds to EGFRvIII which is covalently attached to a oligopeptide containing a D-

amino acid and a positively charged amino acid, carrying an I-125 or I-131 via a 5-iodo-3-pyridinecarboxylate as taught by Reist and Govindan with humanized antibodies which are taught by Emery. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Reist and Govidan on the specific monoclonal antibody which binds specifically to EGFRvIII and the teachings of Emery on the advantages of using humanized antibodies in clinical studies and the methods for making said humanized antibodies.

14. Claims 1, 5, 8-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reist (Cancer Research, 1996) and Govindan (Journal of Nuclear Medicine, May 1998) as applied to claims 1, 5, 8-10, 14 and 17-20 above, and further in view of Miller (Bioorganic & Medicinal Chemistry Letters, 1994). Claims 1, 5, 8-20 are drawn to a composition for internally labeling a cell comprising a ligand which specifically binds to an internalizing cell surface recptor, said ligand being covalently bound to labeled oligopeptide comprising D-Tyr and up to three D-Arg and D-Lys and up to three D-Arg residues. Reist in view of Govidan, as discussed in paragraph 13, does not specifically teach the oligopeptide comprising D-Tyr and up to three D-Arg residues or D-Lys and up to three D-Arg residues. Miller teaches oligopeptide compositions comprising various D-amino acid residues for increasing resistance to cellular proteases (pg 2661, 3rd paragraph). Given the teaching of the prior art on compositions containing D-amino acids as taught by Govidan and various D-amino acid peptides resistant to protease cleavage as taught by Miller and individual compositions for enhancing the residence time of the labeled peptide in the cell as taught by Reist (last paragraph, lines 1-3), it would have been obvious to one of ordinary skill in the art at the time the invention was made to use other D-amino acids collectively for the composition useful for radiolabeling a cell because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as compositions which avoid protease degradation and increase the residence time of the radiolabel in the tumor cell.

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D. KAC

Patent Examiner, Group 1642

May 22, 2000

NANCY A. JOHNSON, PH.D
PRIMARY EXAMINER